Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection 81 (2020) e82–e84

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

CD4+*T*, CD8+*T* counts and severe COVID-19: A meta-analysis ☆

To the editor:

We read an interesting study in your journal. A retrospective study by Liu et al. was conducted to investigate the associated between lymphocyte subset counts and severe COVID-19.[1] They found low counts of CD4+*T* and CD8+*T* were more common in patients with severe COVID-19. And CD4/CD8 ratio showed no significant difference between non-severe and severe COVID-19 groups. CD4+*T* and CD8+*T* play a vital role in maintaining immune function and viral clearance in the body. It has been reported that CD4+*T* and CD8+*T* counts significantly decreased in COVID-19 patients.[2] However, whether their status were correlated with the clinical type of COVID-19 patients has not reached consistent conclusions. Therefore, we conducted this meta-analysis to investigate the relationship between CD4+*T* counts, CD8+*T* counts, CD4/CD8 ratio and the severity of COVID-19 patients.

We searched PubMed, EMBASE and Web of Sciences, using the keywords as "CD4", "CD8", "COVID-19″, "Severe 2019-nCoV", and "SARS-CoV-2″ without date (until Jun 2, 2020) or language restrictions. Trials providing data of counts of CD4+*T*, CD8+*T* or CD4/CD8 ratio in patients with non-severe or severe COVID-19 were included. According to Guidelines for the Diagnosis and Treatment of COVID-19,[3] COVID-19 is classified as mild, moderate, severe, and critical pneumonia. We categorized severe and critical pneumonia into the severe group, mild and moderate pneumonia into the non-severe group. We independently screened every article and extracted the data. Any disagreement were resolved by discussion and consensus. Mean difference (MD) with 95% confidence intervals (95% CI) was calculated in this meta-analysis using Review Manager 5.3 software. Study heterogeneity was assessed using I^2 statistic, when $I^2<50\%$, a fixed-effects model was used, otherwise a random-effects model was chosen. Sensitivity analysis were performed by sequential removal of each trial.

13 studies included a total number of 1647 patients were considered in our meta-analysis. (Supplementary Material) All the studies, except for 1 in Spain,[4] were conducted in China. 10 studies distinguished non-severe and severe groups, 2 studies only reported ICU and non-ICU groups,[4, 5] and 1 study only reported decease and survivor groups.[6] Data of CD4+*T*, CD8+*T* counts and CD4/CD8 ratio were provided in 13, 12 and 8 studies, respectively. Both CD4+*T* and CD8+*T* counts significantly reduced in severe COVID-19 group compared with non-severe group [CD4+*T* (MD: -0.22×10^9/L, 95%CI: -0.27 to -0.17×10^9/L, I^2=89%); CD8+*T* (MD: -0.14×10^9/L, 95%CI: -0.18 to -0.11×10^9/L, I^2=88%)]. There was no significant difference between two groups in CD4/CD8 ratio (MD: 0.17, 95%CI: −0.12 to 0.46, I^2=91%).The details of our meta-analysis are presented in Fig. 1.

COVID-19 is an acute inflammatory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 has a genome sequence 79.6% identical to the SARS-CoV.[7] Similar clinical features, such as fever, dry cough, dyspnoea, and bilateral ground-glass opacities on chest CT scans, were found between COVID-19 and severe acute respiratory syndrome (SARS).[8] It has been reported that low counts of CD4+*T* and CD8+*T* were associated with adverse outcome in patients with SARS, and the counts would rise dramatically when clinical symptoms improved.[9] As Wang et al. reported, after 1 week of COVID-19 treatment, CD8+*T* counts increased only in patients with attenuated symptoms or improved radiological abnormalities, while no similar change of CD4+*T* counts was found.[10] It appears that, unlike SARS, CD8+*T* may be a more sensitive predictor of clinical outcome than CD4+*T* in COVID-19 patients. However, both CD4+*T* and CD8+*T* counts may serve as biomarkers for predicting severity of COVID-19.

There are several limitations in our study. Firstly, the heterogeneity was high across the included studies, though a sensitivity analysis were conducted, it could not see much better. The reason for this phenomenon may be that all of the included studies were retrospective trials, and patients may be at different phase of illness in different studies. Secondly, most of studies were performed in China, limiting the potential application of these conclusion to other regions of the world.

☆ We declare that our work is an original research. It has not been published before and not under consideration for publication elsewhere. In addition, there is no conflict of interest in our research. This article is a meta-analysis, all based on previously published studies, so it is not required ethical approval or patient consent.

https://doi.org/10.1016/j.jinf.2020.06.036

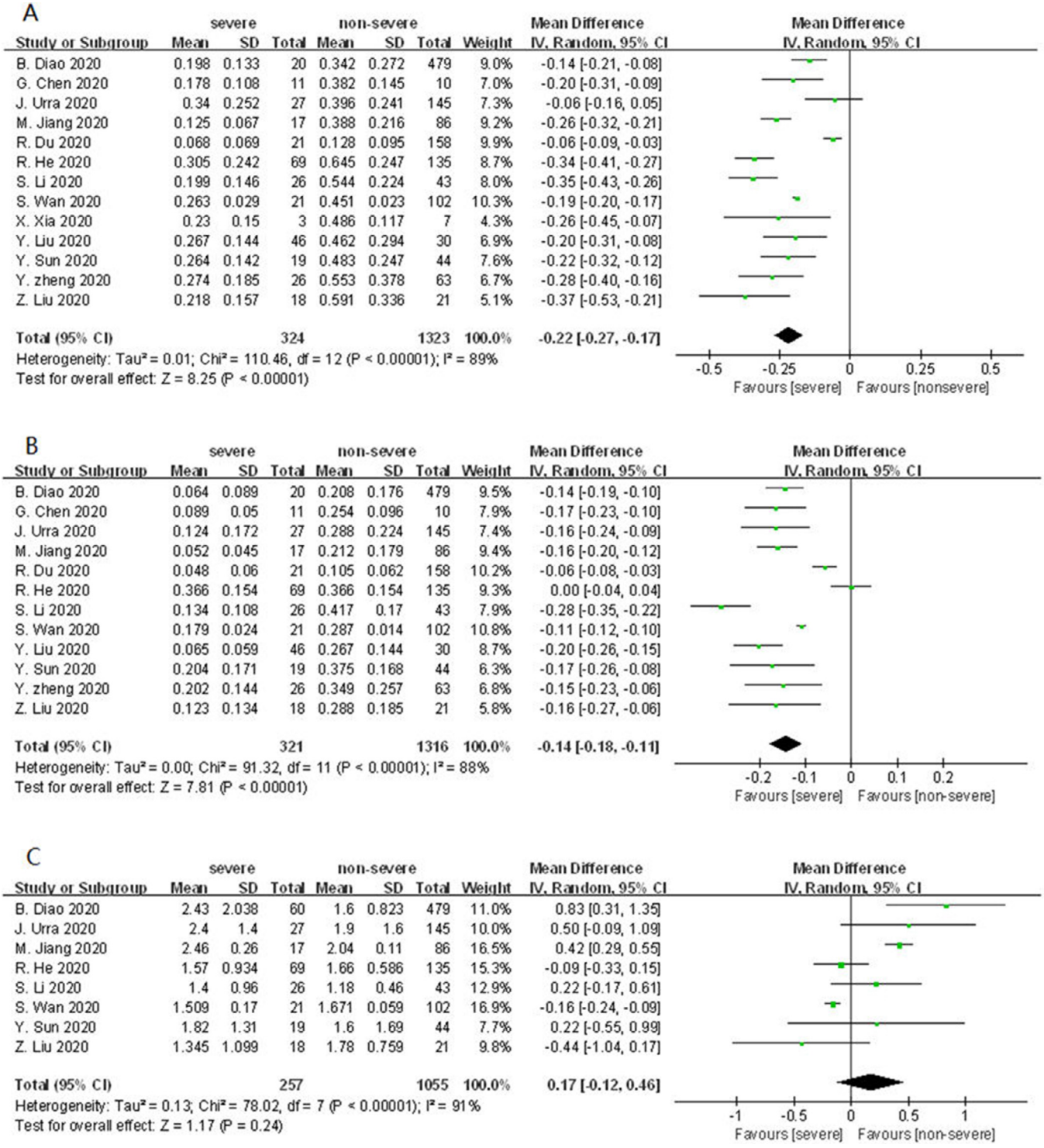

Fig. 1. Mean difference (MD) and 95% confidence interval (95% CI) of counts of CD4+*T*, CD8+*T* and CD4/CD8 ratio in COVID-19 patients with or without severe disease. A, CD4+*T*. B, CD8+*T*. C, CD4/CD8 ratio.

Conflict of Interest

None.

Acknowledgement

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.06.036.

References

1. Liu Z, Long W, Tu M, et al. Lymphocyte subset (CD4+, CD8+) counts reflect the severity of infection and predict the clinical outcomes in patients with COVID-19. *J Infect* 2020. doi:10.1016/j.jinf.2020.03.054.

2. Jiang M, Guo Y, Luo Q, et al. T cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of COVID-19. *J Infect Dis* 2020. doi:10.1093/infdis/jiaa252.
3. National Health Commission of the People's Republic of China. Guidelines for the Diagnosis and Treatment of COVID-19 (Trial Version 7). 2020.http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf. Accessed Jun 16,2020.
4. Urra JM, Cabrera CM, Porras L, et al. Selective CD8 cell reduction by SARS-CoV-2 is associated with a worse prognosis and systemic inflammation in COVID-19 patients. *Clin Immunol (Orlando, Fla)* 2020:108486. doi:10.1016/j.clim.2020.108486.
5. Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). *Clin Transl Immunol* 2020;**11**:827. doi:10.1002/cti2.112810.3389/fimmu.2020.00827.
6. Du R.H., Liang L.R., Yang C.Q., et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. 2020;55(5) doi: 10.1183/13993003.00524-2020
7. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;**579**(7798):270–3. doi:10.1038/s41586-020-2012-7.
8. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**(10223):497–506. doi:10.1016/S0140-6736(20)30183-5.
9. Wong RS, Wu A, To KF, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. *BMJ (Clinical research ed)* 2003;**326**(7403):1358–62. doi:10.1136/bmj.326.7403.1358.
10. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis* 2020;**221**(11):1762–9. doi:10.1093/infdis/jiaa150.

Haipeng Zhang*
Department of clinical laboratory, The Second Hospital of Tianjin Medical University, Tianjin, China. No. 23 Pingjiang Road, Hexi District, Tianjin, China

Ti Wu
Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China. No.154 Anshan Road, Heping District, Tianjin, China

*Correspondence author.
E-mail address: woshizhanghp@sina.cn (H. Zhang)